Treatment with oral bradykinin B2 receptor antagonist deucrictibant immediate-release capsule improves hereditary angioedema attack symptoms

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Introduction

- Approved therapies for hereditary angioedema (HAE) attacks are administered parenterally with substantial treatment burden due to administration time and risk of pain or other injection site reactions[1-4], with treatment of many attacks being delayed or forgone.[5-6]
- An unmet need exists for on-demand oral therapies that are effective and well-tolerated and may reduce the treatment burden enabling prompt administration as recommended by international clinical guidelines.[7-9]
- Deucrictibant immediate-release (IR) capsule (PHVS416) is an investigational formulation containing deucrictibant (PHA121), a highly potent, specific, and orally bioavailable competitive antagonist of the bradykinin B2 receptor.[10-11]
- In the Phase 2 RAPIDe-1 trial (NCT04618211[12]) deucrictibant IR capsule reduced time to onset of symptom relief and to attack resolution measured through the visual analogue scale-3 (VAS-3) and substantially reduced use of rescue medication.[13-14]

Methods

- RAPIDe-1 was a Phase 2, double-blind, placebo-controlled, randomized, crossover, dose-ranging trial of deucrictibant IR capsule for the acute treatment of angioedema attacks in patients with HAE-1/2.
- A primary analysis was performed including 147 qualifying HAE attacks treated by 62 participants with double-blinded placebo or deucrictibant IR capsule 10, 20, or 30 mg (modified intent-to-treat analysis, mITT = all randomized participants with ≥1 treated HAE attack and VAS results at both pre-treatment and ≥1 post-treatment time point).
- Mean Symptom Complex Severity (MSCS) score and Treatment Outcome Score (TOS) are validated composite scores based on patient-reported symptoms of attacks at the affected body sites, included in ecallantide clinical trials[15-17]. Changes in MSCS score and in TOS from pre-treatment to 4 hours post-treatment were secondary endpoints of RAPIDe-1.
- MSCS is a point-in-time measure of symptom severity:
  - Patient-rated severity of each affected symptom on a categorical scale (0 = normal, 1 = mild, 2 = moderate, 3 = severe)
  - Calculated as average score from all affected body sites (symptom complexes)
  - Decrease in score reflects improvement in symptom severity
- TOS is a measure of symptom response to treatment:
  - Patient assessment of response for each affected body site on categorical scale (significant improvement [100], improvement [50], same [0], worsening [-50], significant worsening [-100])
  - Calculated as weighted average of the response at all body sites using pre-treatment severity as weight
  - Increase in score reflects improvement in symptom from pre-treatment
  - Complex Assessment questions evaluate patient-reported change in attack symptoms from pre-treatment (a lot better or resolved – a little better – same – a little worse – a lot worse)

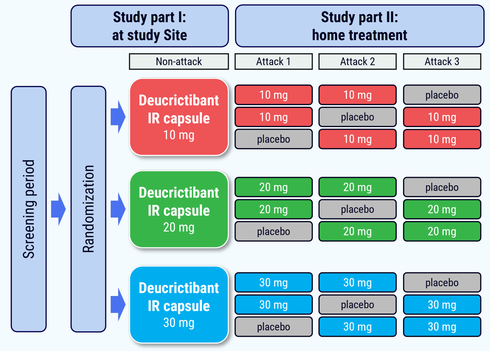

Figure 1. RAPIDe-1 trial design schematic

Results

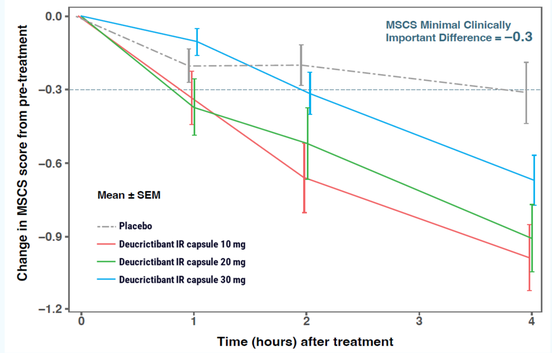

Figure 2. MSCS score measured up to 4 h post-treatment

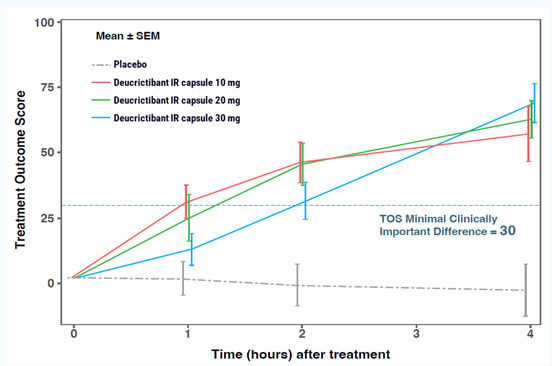

Figure 3. TOS measured up to 4 h post-treatment

	Placebo	Deucrictibant IR capsule 10 mg	Deucrictibant IR capsule 20 mg	Deucrictibant IR capsule 30 mg
Number of patients with post-treatment TOS PRO	49	21	16	19
Number of attacks with post-treatment TOS PRO	49	36	28	29
Attacks with onset of all symptom complexes "**a little better**" within 48 hours – n (%)	18 (36.7%)	32 (88.9%)	25 (89.3%)	27 (93.1%)
Median (95% CI) time (hours) to **onset of symptom relief** by KM estimate	7.62 (3.95, -)	1.89 (0.97, 3.97)	2.15 (1.75, 4.00)	1.98 (1.80, 3.87)

Onset of symptom relief = The time point when TOS PRO first reaches at least "A little better" for all symptom complexes affected at baseline, and no new symptom in any other symptom complex is reported. Relief is confirmed if the improvement is sustained at 2 consecutive time points.

Table 1. Time to onset of symptom relief measured through TOS

	Placebo	Deucrictibant IR capsule 10 mg	Deucrictibant IR capsule 20 mg	Deucrictibant IR capsule 30 mg
Number of patients with post-treatment TOS PRO	49	21	16	19
Number of attacks with post-treatment TOS PRO	49	36	28	29
Attacks with onset of all symptom complexes "**a lot better or resolved**" within 48 hours – n (%)	13 (26.5%)	30 (83.3%)	23 (82.1%)	25 (86.2%)
Median (95% CI) time (hours) to **almost complete or complete symptom relief** by KM estimate	23.28 (5.78, 47.17)	4.02 (3.93, 5.77)	5.93 (3.90, 8.58)	4.12 (3.92, 7.22)

Almost complete or complete symptom relief = The time point when TOS PRO first reaches "*A lot better or resolved*" for all symptom complexes affected at baseline, and no new symptom in any other symptom complex is reported.

Table 2. Time to almost complete or complete symptom relief measured through TOS

Conclusions

- **In the Phase 2 RAPIDe-1 trial deucrictibant IR capsule improved symptoms and reduced time to symptom relief and to resolution of HAE attacks**
- **Clinical meaningful improvement of symptoms was observed during the first hours after treatment with deucrictibant IR capsule**
- **The U.S. FDA has placed a hold on clinical trials of deucrictibant for long-term prophylaxis in the United States of America. For the latest information and updates visit: https://ir.Pharvaris.com/.**

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